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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/690,435 | 10/21/2003 | Mark F. Pittenger | 640100.470 | 3718 |

7590 07/17/2007
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| EXAMINER |
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SAJJADI, FEREDOUN GHOTB

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| ART UNIT | PAPER NUMBER |
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1633

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07/17/2007

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/690,435

Applicant(s)

PITTENGER ET AL.

Examiner

Fereydoun G. Sajjadi

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 June 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: 16 and 21.
Claim(s) rejected: 1-10 and 12-28.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because:
See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
13. ☐ Other: _____.

Advisory Action

Continuation of 11. does NOT place the application in condition for allowance because:

The objection to claims 16 and 21, as failing to further limit the subject matter of claims 12 and 17, respectively, is maintained for reasons of record. Claims 12 and 17 recite “autologous or allogeneic”. Autologous cells are derived from the same individual and allogeneic cells are derived from the same species. Therefore the recitation of “allogeneic” in dependent claims 16 and 21 is broader than the limitation of “autologous”, as a species encompasses more than one individual.

The examiner maintains the rejection of claims 1, 2, 4-10 and 12-21 under 35 USC 112, second paragraph. Applicants’ argument that it is clear that what is claimed is a method of producing cardiomyocytes in a heart, improving ventricular wall motion of the heart or stimulating or promoting angiogenesis in the heart of the individual, is not found persuasive. While the intended use of the methods is to produce cardiomyocytes, or repair or regenerate blood vessels in the heart, the language contained in the body of the claim makes it unclear whether the cardiomyocytes are actually produced in the heart or elsewhere in the body. That the claims recite “administering to the heart of an individual” should only be considered a suggestion, as to clarify the claim language at issue.

The rejection of claims 12-21 under 35 USC 112, first paragraph, scope of enablement, is maintained for reasons of record. Applicants argue that Example 7 states that MSCs are associated with the smooth muscle layer of a blood vessel and that such cells expressed factor VIII and VEGF, not expressed in cultured MSCs; concluding that the MSCs did contribute to the formation of blood vessels in the heart. Such is not persuasive, because such a conclusion would be premature in view of the fact that the specification does not show the production of any vascular cell, or any evidence for the formation of arteries, veins and capillaries, formed as a result of administering MSCs to the heart. Localization and association with the smooth muscle layer is not synonymous with repair or regeneration of blood vessels or the promotion of angiogenesis, as the amount or sufficiency of the expressed factors cannot be determined. The association of the MSCs may be with blood vessels already present in the heart tissue. Therefore, it remains unclear whether transplanted adult MSCs of the instant invention resulted in the repair

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and regeneration of blood vessels, as even the indirect contribution of the MSCs in providing angiogenesis promoting factors cannot be determined in an environment where such factors are continually supplied by various cells and tissues.

In response to Applicants' argument that the Examiner has provided no evidence, other than sheer speculation, that methods of administration other than direct administration of the MSCs to the heart would not be effective in repairing or regenerating blood vessels in the heart, it should be noted that the enabled scope previously indicated in the office action of 9/22/2006 did not indicate an enablement for MSC mediated "repairing or regenerating blood vessels in the heart", regardless of the route of administration. Furthermore, the instant claims have been examined in accordance with the *Wands* factors, and in view of the teachings of the post-filing art of record, the high level of unpredictability in transplantation and differentiation of MSCs, and the lack of guidance provided by the specification, it is concluded that the specification does not enable a person of skill in the art to make and use the invention without undue experimentation. Therefore, it is maintained that the specification does not provide an enabling disclosure for repairing or regenerating blood vessels, or a method of stimulating or promoting angiogenesis in the heart of an individual, or where MSCs (or genetically modified MSCs) are administered by any route to said individual. Thus, the rejection of claims 12-21 is maintained for reasons of record and the foregoing discussion.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is (571) 272-3311. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Fereydoun G. Sajjadi, Ph.D.

Examiner

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/Anne Marie S. Wehbe/

Primary Examiner, A.U. 1633